APOE Gene e4 Allele Accelerates the Atrophy of the Inferior Temporal Lobe in Alzheimer's Disease (BIOORGANIC CHEMISTRY-Molecular Clinical Chemistry)

AUTHOR(S):

Tanaka, Seigo; Ueda, Kunihiro

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Seigo Tanaka and Kunihiro Ueda

The apolipoprotein E (*APOE*) gene ε4 allele is a genetic risk factor for late-onset familial and sporadic Alzheimer's disease (AD). The change in size of the whole brain or total ventricular system did not differ significantly among *APOE* genotypes. The patients with ε3/ε4 or ε4/ε4 genotype (ε4+ group), however, exhibited severe atrophy in the inferior temporal lobe, while those with ε3/ε3 genotype (ε4- group) showed mild atrophy. Regional cerebral blood flow (rCBF) in the cerebral cortex, particularly in the temporal lobe, was lower in the ε4+ group than in the ε4- group. These results indicate that possession, and thus expression, of the *APOE* ε4 allele preferentially affects the inferior temporal lobe, encompassing the hippocampus and amygdala, in AD patients.

Keywords : Apolipoprotein E / X-ray CT / MRI / Xe-133 SPECT / Hippocampus / Amygdala

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder in senescence presenting as progressive dementia. It is pathologically characterized by βA4 amyloid deposition in senile plaque cores and cerebral vessels. In our previous study on Japanese sporadic AD patients [1], we confirmed the association between apolipoprotein E (*APOE*) gene ε4 allele and late-onset AD. In the present study, we approached the issue of how *APOE* genotype affects the progression of the disease by analyzing AD brains with X-ray computed tomography (CT), magnetic resonance imaging (MRI) and Xe-133 single photon emission CT (SPECT) [2].

I. X-ray CT Findings and *APOE* Genotypes

We estimated the whole brain atrophy and ventricular dilatation by using X-ray CT. A comparison between control and AD revealed a significant difference in the size of the cerebral hemispheres and ventricular systems. However, there was no significant difference in these areas among AD subgroups of different *APOE* genotypes. A retrospective study revealed that the progress of cerebral atrophy along the clinical course was not significantly faster in patients with ε3/ε4 or ε4/ε4 genotype than in those with ε3/ε3 genotype. Thus the ε4 allele does not appear to accelerate atrophy of the brain as a whole in the course of the disease.

BIOORGANIC CHEMISTRY — Molecular Clinical Chemistry —

Scope of research

This laboratory was founded in 1994 with the aim of linking (bio)chemical research and clinical medicine. Thus, the scope of our research encompasses the structure, function and regulation of various biomolecules, the pathophysiological significance of bioreactions in relation to human diseases, and the application of molecular techniques to clinical diagnosis and therapy. Our current interest is focused on poly(ADP-ribosyl)ation, nuclear (de)localization of proteins in association with apoptosis, and the molecular etiology of Alzheimer's disease and related disorders.

Prof
UEDA, Kunihiro
(D Med Sc)

Assoc Prof
TANAKA, Seigo
(D Med Sci)

Instr
ADACHI, Yoshifumi
(D Med Sci)

Guest Scholar
BANASIK, Marek (D Med Sci)
Guest Rec Assoc
STROSZNAJDER, Robert (Ph D)
Students
MINAKUCHI, Masayoshi (DC)
MATOH, Naomi (DC)
SHO, Toh (DC)
TAKANO, Emiko (RF)
KITAGAWA, Koichiro (RF)
WILLIAMS, Tyler (RS)
TAKEHASHI, Masanori (RS)

II. MRI Findings and *APOE* Genotypes

We focused further analysis on the inferior temporal lobe, including the hippocampus and amygdala. This region is known to be severely affected in AD and responsible for memory impairment and cognitive decline. MRI allowed clear visualization of this region. As a distinct finding, AD patients with ε3/ε4 or ε4/ε4 genotype exhibited severe atrophy in this region, while those with ε3/ε3 showed milder atrophy (Figure 1). Atrophy of this region accompanied dilatation of the temporal horn of the lateral ventricle. The atrophic change in the inferior temporal lobe was more marked on the medial side, which encompasses the limbic system, such as the hippocampus and amygdala. We analyzed the association of the size of this region with *APOE* genotypes and found a difference among AD subgroups (Figure 2). These results indicate that the *APOE* ε4 allele promotes atrophic change in the brain preferentially in the inferior temporal lobe.

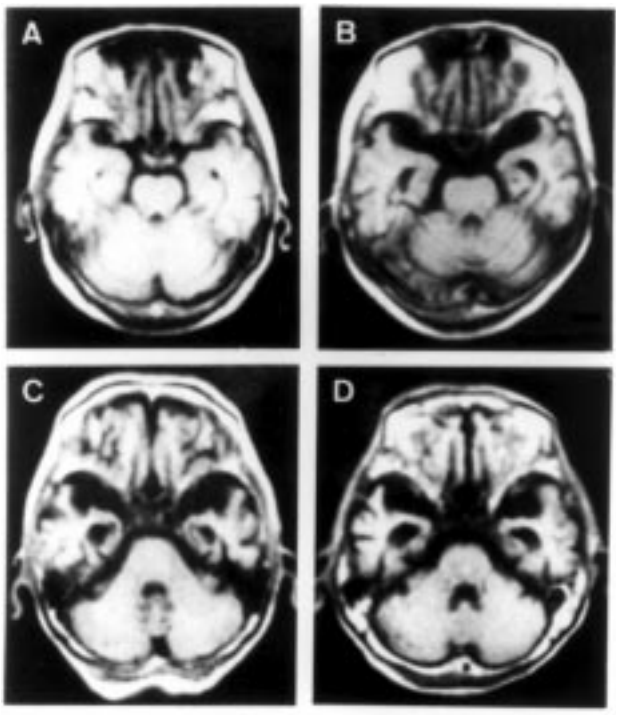

Figure 1. Findings of MRI at the level of the pons. No atrophy was observed in the inferior temporal lobe of the control subject (A). Patients with ε3/ε3 (B), ε3/ε4 (C) and ε4/ε4 (D) genotypes showed mild, moderate or severe atrophy, respectively.

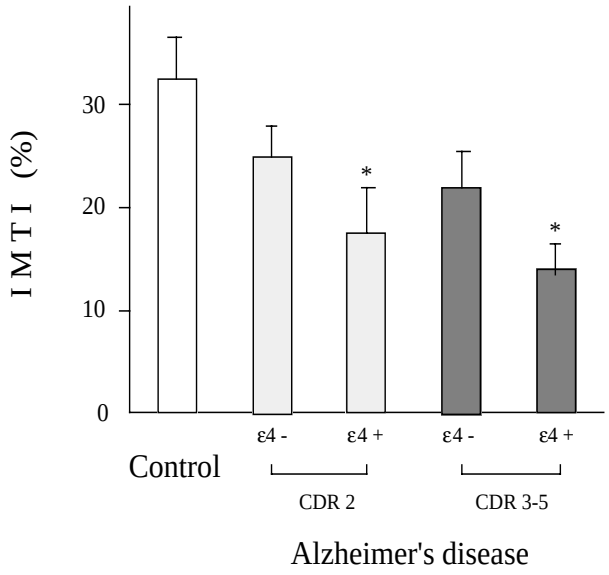

Figure 2. Infero-medial temporal index (IMTI) of control subjects and AD patients. The patients were classified into subgroups of CDR (Clinical Dementia Rating) 2 (moderate) and CDR 3-5 (severe) with *APOE* genotype, ε4- or ε4+.
* $p < 0.05$, as compared with the ε4- group (unpaired *t* test).

III. Xe-133 SPECT Findings and *APOE* Genotypes

In addition to the morphological analysis by X-ray CT and MRI, we assessed a functional change of AD brain by Xe-133 SPECT. The mean value of the regional cerebral blood flow (rCBF) was significantly lower in AD than in control in all cerebral regions except for the occipital lobe. Among the AD subgroups, the rCBF was lower in patients with ε3/ε4 or ε4/ε4 genotype than those with ε3/ε3; the difference was statistically significant in the temporal lobe. In view of the fact that rCBF reflects a functional activity of the brain, the reduction of rCBF indicates an impaired brain function. A reduction of rCBF might be caused by the deposition of vascular amyloid, which was reported to be severe in patients with the *APOE* ε4 allele.

References

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